

Factors Influencing the Cost-Effectiveness Outcomes of HPV Vaccination and Screening Interventions in Low-to-Middle-Income Countries (LMICs)

Okeah, Bernard O; Ridyard, Colin H

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Factors influencing the cost-effectiveness outcomes of HPV vaccination and screening interventions in Low-to Middle-Income Countries (LMICs): A systematic review

Author Information

Affiliations

School of Healthcare Sciences, Bangor University, Bangor, Gwynedd, LL57 2EF. UK

Bernard O Okeah

Centre for Health Economics and Medicines Evaluation, Bangor University, Normal Site, Bangor, Gwynedd, LL57 2PZ. UK

Colin H Ridyard PhD

Contributions

B.O. conceived the idea, designed the study protocol and was the first reviewer. C.R. verified the study protocol, was the second reviewer and supervised the study. The authors discussed the findings of this study and contributed to the final report.

Corresponding author

Correspondence to Colin H Ridyard

E-mail: c.h.ridyard@bangor.ac.uk

Phone: 01248 388861

Factors influencing the cost-effectiveness outcomes of HPV vaccination and screening interventions in Low-to Middle-Income Countries (LMICs): A systematic review

Abstract

Background: Cervical cancer ranks fourth amongst the commonest malignancies worldwide and the second most prevalent cancer afflicting women in low-to middle-income countries (LMICs), hence, of great public health importance. LMICs are the most affected regions as evidenced by their high prevalence of the disease. Mortality associated with cervical neoplasms is preventable through the implementation of recommended preventive approaches.

Aims: This review aimed at appraising evidence on the cost-effectiveness of cervical cancer prevention interventions in LMICs involving cervical screening and HPV vaccination programmes.

Methods: A search of CINAHL, MEDLINE, PubMed, and Web of Science was elicited and studies published between 1st January 2008 and 31st December 2018 were retrieved. Two authors independently undertook the screening, review, selection of studies, and data extraction with disagreements being resolved through discussion and consensus.

Results: Twelve studies were selected. The cost-effectiveness outcomes of HPV vaccination and screening interventions are dependent on age, screening method used, intervention coverage, and the number of doses or visits required for vaccination and screening respectively. A combination of visual inspection with acetic acid (VIA) screening and HPV vaccination appears to be the most cost-effective approach in reducing the lifetime risk for HPV-linked cervical neoplasms. Similarly, vaccination as a stand-alone intervention is potentially cost effective provided the coverage is maintained between 70-100%.

Conclusions: HPV vaccination and screening interventions may be cost-effective in LMICs and potentially reduce the lifetime risk, economic burden, and associated mortality. However, it is important to consider the factors that influence the cost-effectiveness of cervical cancer prevention interventions for better outcomes to be realised.

Key points for decision makers

- HPV vaccination and VIA screening appear to be cost-effective approaches for reducing the lifetime risks for cervical cancer in LMICs
- A high loss-to-follow-up for vaccination and screening is associated with increased mortality
- Early screening for HPV below the age of 30 years could potentially reduce cervical cancer associated morbidity and mortality
- Implementation of organised programmes improves coverage and has better outcomes compared to opportunistic programmes

Introduction

Cervical cancer ranks fourth among the more ubiquitous global malignancies and is the second most prevalent cancer afflicting women in low-to middle-income countries (LMICs), thus, representing a significant public health challenge (1). It represents an estimated 6.6% of all neoplasms in women (2) with over 550,000 new cases and 311,365 fatalities reported in 2018 (2,3). This figure is higher than the cervical cancer-linked mortality of approximately 266,000 deaths reported in 2012 (4) and 270,000 deaths recorded in 2015 (5).

LMICs have a higher burden of cervical carcinoma recording more than two thirds of global cases and 90% of all associated deaths (6). Future projections suggest a potential rise in cancer cases amongst women by 0.11% in 2035 while that of males will drop by 0.03% (7). Despite these facts, countries bearing the highest burden of cervical carcinomas utilize only 5% of all resources spent on the disease (5).

Healthcare systems in most LMICs are fragmented and present many challenges which limit women's access to treatment interventions (5). Many countries lack well organized programmes for cervical cancer mitigation with financial constraints further limiting access to relevant interventions; thus, , causing up to an 18 times greater mortality rate in comparison to developed countries (3). Cervical cancer propagates the cycle of poverty and undermines economic development in affected communities.

An association exists between human papilloma virus (HPV) infections and cervical cancer (8), which account for 15.4% of all carcinomas linked to infections within sub-Saharan Africa (9). There exists clinically effective vaccines against the oncogenic strains of HPV (10) but these are not freely available in most LMICs (6). Lack of government prioritization in LMICs limits access to life saving preventive interventions for women.

Early detection of cervical neoplasms is a major prognostic factor and improves women's survival rate (11). Deaths and disability occasioned by cervical cancer are preventable through multidisciplinary and comprehensive interventions delivered across the lifespan to ensure their cost-effectiveness (5,12,13). The WHO's comprehensive approach to controlling cervical carcinoma provides for primary, secondary, and tertiary prevention measures such as vaccination, screening, and post-treatment follow-up services respectively (12,14).

A quick scoping of existing literature on the current research question retrieved two systematic reviews undertaken in LMICs. The first review (15) mainly focussed on HPV vaccination with minimal attention paid to screening interventions. Notably, the conclusions made by Fesenfeld, Hutubessy, and Jit, (2013) only centred around the implications of model types, vaccine prices, and vaccinating boys on cost-effectiveness outcomes. A second systematic review (16) focussed on how decision models utilized in HPV vaccination programmes account for the apparent challenges in LMICs.

The evidence regarding the most suitable strategies for preventing cervical neoplasms and the specific factors influencing the cost-effectiveness of such interventions is not comprehensive. Notably, the preferences for screening or vaccination approaches varies across LMICs and consistency in practice appears to be lacking. There is therefore a need to consolidate evidence on the interventions and optimize resource allocation for preventing cervical neoplasms in LMICs.

This systematic review (SR) comparatively investigates the factors influencing the cost-effectiveness outcomes of both screening and vaccination interventions. Furthermore, the review appraises the available economic evidence on the cost-effectiveness of HPV screening programmes in LMICs not addressed by previously undertaken studies. Lastly, the

researchers explore the cost-effectiveness for combining various HPV screening approaches with HPV vaccination in LMICs. The findings are of significance to health policy formulators as well as health practitioners involved in mitigation of cervical carcinomas.

Research questions

1. What factors influence the cost-effectiveness outcomes of HPV vaccination and screening in LMICs?
2. Are HPV screening interventions cost-effective in LMICs?
3. Which screening approach is the most cost-effective when combined with HPV vaccination in LMICs?

Methods

The study adopted a systematic review design in answering the research questions. The reporting was undertaken in compliance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement (17). A protocol for this systematic review is available on request through the authors' email addresses

(bernardokeah@gmail.com or c.h.ridyard@bangor.ac.uk).

Table 1 below outlines the PICO (Population, Intervention, Control, Outcomes) framework that was adopted to facilitate a literature search across databases using appropriate medical subject headings (MeSH) (18). The review targeted cost-effectiveness studies assessing HPV vaccination and screening in LMICs. Grey literature and unpublished studies were excluded from this review to avoid their potential effect on results synthesis (19).

Table 1: PICOS framework

Population	The population for the HPV vaccination comprised of Girls and boys from (low-to-middle income countries (LMICs) aged between 9-15 years. The population for cervical cancer screening comprised of women from LMICs aged between 20-69 years
Intervention	HPV vaccination and/or routine screening through visual inspection with acetic acid (VIA), cytology, or Pap smear
Control	No intervention or vaccination only, or screening only.
Outcomes	i. Reduction in the incidence and mortality associated with cervical neoplasms ii. Incremental Cost-Effectiveness Ratio (ICER) iii. Incremental costs.
Study Design	Cost-effectiveness analysis studies

CINAHL, MEDLINE, PubMed, and Web of Science were searched between 15th July 2019 and 25th July 2019. Only studies published in English, between 1st January 2008 and 31st December 2018 were included. Search terms applied included developing countr*, low-income countr*, screen*, monitor*, check*, VIA, cervical cancer, cervical neoplasm*, HPV,

vaccine*, cost-effective* and cost-utility. Boolean operators ‘OR’ and truncation (*) to were useful in expanding the search whereas “AND” was utilized in limiting the searches.

Appendix 1 below provides the full search strategy and the limiters as applied in the MEDLINE database.

Eligibility assessment commenced with the screening of the article titles after which the abstract and the entire article were read to ascertain consistency with the inclusion criteria outlined in the PICOS framework. The selection process also entailed an assessment of the methodological rigour of the studies.

A Microsoft excel data extraction sheet was piloted using two randomly selected articles and refined based on the pilot outcome (20,21). The extraction process followed a systematic process to minimize errors and enhance the quality of the findings. The extracted data was checked against the checklist and inclusion criteria to ensure its completeness and accuracy.

Information extracted included the type of economic evaluation undertaken, the study perspective as well as the key assumptions. Additional data included the study population, the interventions, and the nature of the study whether model-based or empirical studies. The extraction also included the source of the cost measures, costing approach, the reference year, type of costs included, benefits accrued, sensitivity analysis undertaken, the cost-effectiveness threshold, the ICERs, the study conclusions, and the declaration of funding as well as any conflicts of interest.

The Drummond and the CHEC (consensus on health economics criteria) checklists were employed in assessing the risk of bias (RoB) (20,22). The RoB was useful in ascertaining any significant variations with respect to the cost-effectiveness of the interventions. The assessment also focussed on the transparency and clarity in reporting cost components (23). Following the RoB assessment, studies were excluded based on their

transparency. Studies that did not report on the relevant parameters as outlined in the CHEC checklist were deemed as lacking transparency and excluded from the review.

Summary measures included the incremental costs for HPV vaccination and cervical cancer screening as well as the ICER (24). Additional measures included the benefits reported across studies such as the effect of the interventions on the lifetime risk as well as the mortality linked with cervical carcinomas.

Two authors independently undertook the screening, review, selection of studies, and data extraction with disagreements resolved through discussion and consensus. This review provides a narrative synthesis of the results and does not constitute a meta-analysis of the study findings. The costs and benefits are reported in a uniform currency of international dollars (I\$) by applying the purchasing power parity exchange rates (25) and discounted at 3% to 2017 as the base year.

Results

Study selection

The figure 1 below summarizes the process for identifying, screening, and selecting of studies for the present systematic review

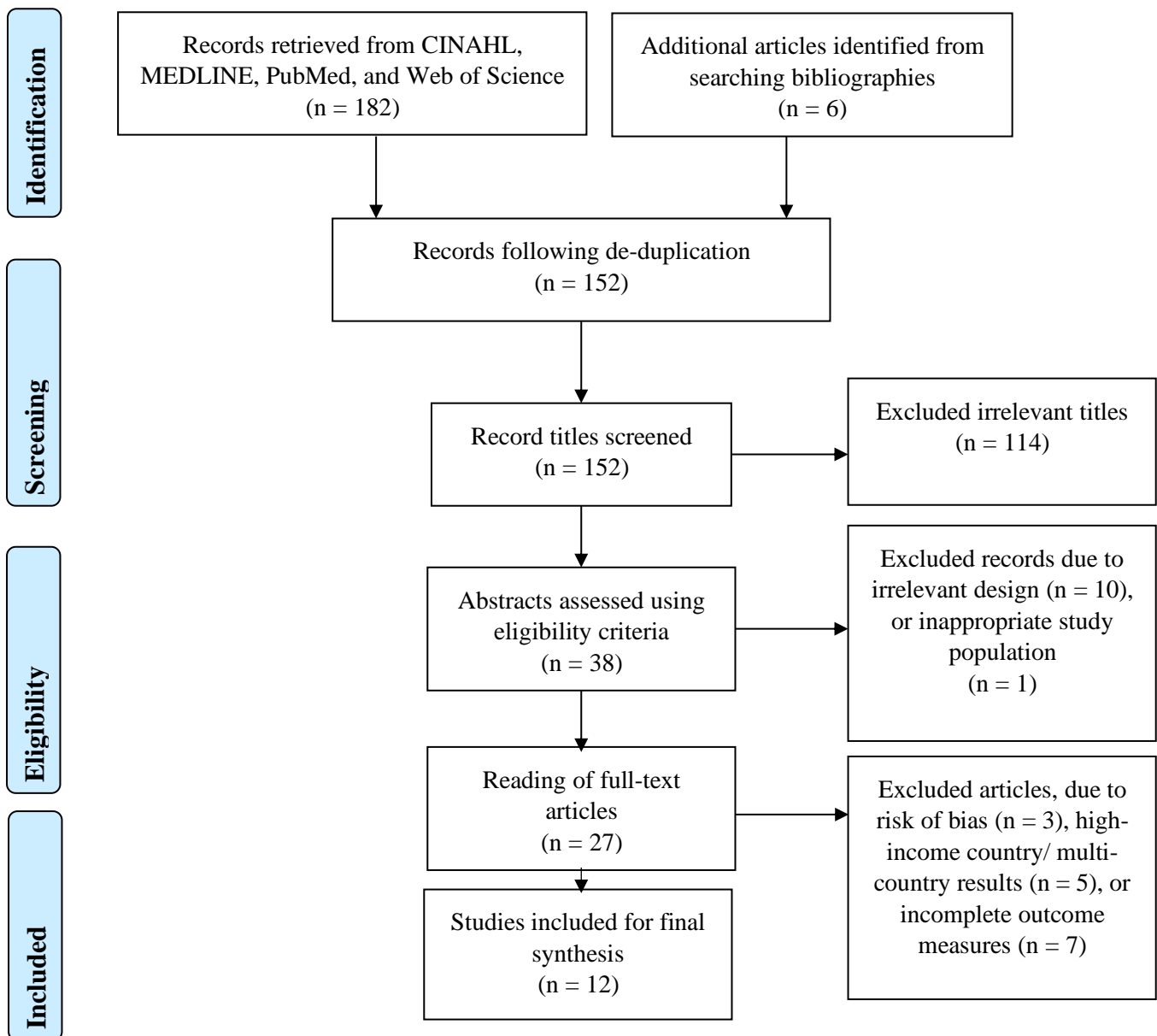


Figure 1: PRISMA flow chart summarizing the process for selecting studies

The literature search yielded 188 studies and 152 studies after deduplication. Following title review, 114 studies were excluded whereas a further 11 articles were discarded following abstract review. Twelve articles were excluded after full text reading and a further three articles excluded after assessing the RoB, reporting transparency, as well as their transferability. Finally, this review included twelve (12) studies that met the stated criteria.

Study characteristics

The review provided eleven cost-effectiveness analysis (CEA) studies and one cost-utility analysis (CUA) study published. All the retrieved studies originated from LMICs namely Thailand, Colombia, Uganda, Laos, Malaysia, Iran, China, Honduras, India, South Africa, and Brazil as shown in Figure 2. All the retrieved studies were model-based and relied on published data for model calibration.

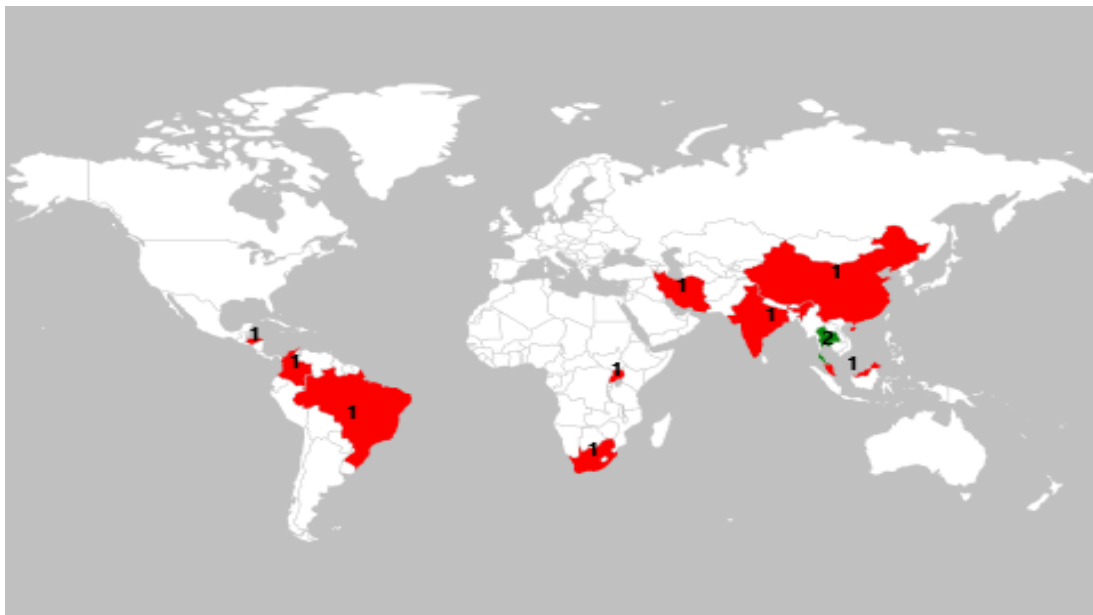


Figure 2: Distribution of selected studies per country

The studies were modelled on hypothetical participants and their age ranges depended on the intervention type. The participants included females aged 9-15 years for the HPV vaccination interventions and 21-69 years for screening interventions while one study

explored the potential benefit of vaccinating boys. The interventions reported in the included studies were HPV vaccination in combination with screening (8,26–29), HPV vaccination only (30–33), and screening only (34–36).

The outcomes of the interventions reported include a reduction in the cervical carcinoma incidence, improvement in the quality of life and mortality reduction. The authors reported the cost-effectiveness of the interventions by comparing the ICERs with the per capita GDP per capita as proposed by the WHO's Commission for Macroeconomics and Health (37–39). Interventions whose ICERs fall below the per capita GDP (1XGDP per capita) are highly cost-effective while those that do not surpass two times the GDP (2XGDP) are very cost-effective. Lastly, interventions whose ICERs fall below three times the per capita GDP (3XGDP per capita) are considered cost-effective. Based on these measures, four of the interventions were highly cost-effective whereas half of the interventions surpassed the cost-effectiveness threshold, while two did not.

Table 2: Summary of study characteristics

Author	Country	Population	Age	Intervention	Empirical- or model- based EE	Comparator(s)	Outcome measure(s)	Perspective	Intervention cost- effectiveness	Competi ng interests	Funding
Andres-Gamboa et al. (34)	Colombia	Girls	21-69	Screening: Cytology or HPV DNA	Model	No screening	YLS	Payers perspective	Cost-effective	None declared	Not stated
Campos et al., (35)	Uganda	Women	>35	Screening: VIA or HPV DNA	Model	No screening	YLS	Societal	Cost-effective	Declared	NCI and B&MGF
Chanthavilay et al. (28)	Laos	Women Girls	10	Vaccination plus screening	Model	Screening only or vaccination only	DALYs	Public healthcare	Cost-effective	Declared	AUF
Ezat and Aljunid (8)	Malaysia	Women	>18	Vaccination plus screening	Model	Screening only	QALYs	Public healthcare	Cost-effective	None declared	Not stated
Khatibi et al. (30)	Iran	Girls	15	Vaccination	Model	No vaccination no screening	QALYs	Government	Not cost-effective	Declared	Not stated
Levin et al. (36)	China	Women	35-45	Screening: HPV DNA	Model	Screening: Cytology	YLS	Societal	Cost-effective	Declared	B&MGF
Molina et al. (33)	Honduras	Girls	11	Vaccination	Model	No vaccination, no screening	DALYs	Societal and government	Highly cost-effective	Declared	B&MGF
Prinja et al. (32)	India	Girls	11	Vaccination	Model	Treatment of unvaccinated	QALYs	Societal and government	Highly cost-effective	None declared	Not stated
Sharma et al. (26)	Thailand	Girls	>9 years	Vaccination plus screening	Model	Screening	YLS	Societal	Cost-effective	None declared	B&MGF
Sinanovic et al. (27)	South Africa	Girls Women	>12 >30	Vaccination & screening	Model	Screening: Cytology	QALYs	Societal	Highly cost-effective	Declared	B&MGF
Termrungruanglert et al. (31)	Thailand	Girls	>12	Vaccination	Model	No vaccination	QALYs	Healthcare provider	Cost-effective	Declared	Not stated
Vanni et al. (29)	Brazil	Girls Women Boys	10, 25-60	Vaccination & screening	Model	Screening: Cytology	QALYs	Health system	Cost-effective	None stated	Not stated

AUF Agence Universitaire de la Francophonie, B&MGF Bill & Melinda Gates, DALYs Disability-adjusted-life-years, NCI National Cancer Institute, QALYs quality-adjusted-life-years, YLS years of life save

Risk of bias (RoB) within the selected studies

Table 2 below summarizes the risk of bias assessment using the CHEC checklist as proposed by Wijnen et al., (2016) .

Table 3: Risk of bias in the selected studies

	CHEC items	Andres-Gamboa et al. (34)	Camp os et al., (35)	Chantha vilay et al. (28)	Ezat and Aljunid (8)	Khatib i et al. (30)	Levi n et al. (36)	Molina et al. (33)	Prinja et al. (32)	Sharm a et al. (26)	Sinano vic et al. (27)	Termrung ruanglert et al. (31)	Vanni et al. (29)
1	Clearly defined population	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
2	Clearly defined comparator	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
3	Research question	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
4	Appropriate design	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
5	Valid assumptions	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
6	Appropriate time horizon	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
7	Perspective chosen	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
8	All costs included	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
9	Appropriate cost measures	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
10	Appropriate cost valuation	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
11	All outcomes identified	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
12	Measured all outcomes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
13	Outcomes valued correctly	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
14	ICERs/ ICURs calculated	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
15	Discounted costs and benefits	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
16	Sensitivity analysis	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
17	Conclusions linked to results	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
18	Generalizability discussed	No	No	No	No	No	No	No	No	No	No	No	No
19	Competing interests declared	No	Yes	Yes	No	No	Yes	Yes	No	No	Yes	Yes	No
20	Funding disclosed	No	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Yes	No	No

Results synthesis

There were significant differences across the selected studies, hence, this review focussed on describing the results, and their application rather than undertaking a meta-analysis of key findings. The study population for both screening and vaccination interventions was predominantly female while only one study included males (29). The latter findings revealed that including males makes HPV vaccination intervention non cost-effective (29).

HPV vaccination

Eleven studies reported vaccinating girls aged 9-13 years was highly cost-effective; however, one study found otherwise but assumed a low coverage and a very high cost of vaccines (30). Regarding the number of doses required to achieve lifelong immunity against HPV, four studies assessed the effectiveness of vaccination with three doses (27,28,30,33). Two more studies assessed the use of two doses of vaccination (29,32) while another two studies focused on single dose vaccinations (26,31). Determining the number of vaccine doses that produced the best cost-effectiveness results was beyond the scope of this review.

Furthermore, the vaccine efficacy significantly influences cost-effectiveness outcomes for vaccination programmes (26,31,32). The findings suggest that HPV vaccination interventions have potential cost-effectiveness in LMICs. Vaccination without any other intervention appears to be very cost effective (ICER I\$3.19-821.85/ QALY/ DALY) provided the coverage is maintained between 70-100% based on the reviewed evidence (32,33). However, an Iranian-based study determined that three dose vaccination was not cost-effective (I\$15608.94/QALY) (30).

HPV Screening

The reported age range for screening was 21-69 years (34), 35 years (35), and 35-45 years (36). Notably, two of the included studies reported initiating screening at an early age (below 30 years) improved cost-effectiveness (28,34). The screening approaches also varied across studies and included VIA (26–28,35), HPV DNA testing (26–28,34–36), and cytological analysis or Pap smear (8,26–29,34,36). Cost-effectiveness varied significantly when drawing comparisons based on the screening approaches used.

The number of visits required to complete a screening test is important because the associated loss-to-follow-up (LTFU) undermines the overall effectiveness of screening interventions. HPV DNA analysis appears to be less cost-effective whenever the LTFU exceeds 40% of the primary population (28,34). Notably, reducing the uptake of follow-up services may contribute to a higher mortality rate in comparison with low coverage with respect to screening interventions.

The reviewed evidence shows that screening interventions may not be cost-effective at lower coverage but are cost-effective at 50% coverage and become very attractive options at a coverage of 70% of the population at risk. In addition, the findings reveal that organized cervical cancer prevention programmes achieve a higher coverage of the population at risk than opportunistic programmes and result in better cost-effectiveness outcomes than opportunistic interventions (28,34).

The cost range for VIA screening was I\$3.65-I\$55.81 whereas HPV DNA testing and cytological analysis across costs ranged between I\$9.0-I\$229.93 and I\$3.74-I\$69.20 respectively. The ICERs reported in different studies varied widely with two studies reporting that screening with no other intervention was cost-effective (34,35). The implementation of two visit HPV DNA testing appears to be very cost-effective recording an ICER of

I\$105.21/YLS (36). When the loss-to-follow-up is below 40%, HPV DNA testing appears to yield higher cost-effectiveness when compared with other methods (35). Otherwise, there is a 73% probability that VIA will be more cost-effective screening strategy in comparison with HPV DNA testing when implemented (28).

Table 4: Summary of individual study results

	Intervention	Frequency/ Doses	Coverage	Efficacy/ sensitivity	Reference year	Cost (Original)	ICER (Original)	Discounted costs (I\$)	Discounted ICERs (I\$/)	Remarks
SCREENING ONLY										
Andres-Gamboa et al. (34)	Cytology	3x	50-100%	72.7(50-81.5)%	2007	\$6.34(5.9-12.67)		4.72		
	HPV DNA	2x	50-100%	90(86.4-93.7)%		\$12.10(8.30-62.53)	USD\$44/YLS	9.00	32.74	Very cost-effective
Campos et al. (35)	VIA	1x	30-100%	40-60%	2005					
	HPV DNA	2x	30-100%	70-90%		\$17.06–19.07	I\$300/YLS	11.97-13.38	210.41	Cost-effective
Levin et al. (36)	HPV DNA	2x		89.7(50-100)%	2005	\$45.89	\$80-150/YLS	32.19	105.21	Very cost-effective
	Cytology			63(50-100)%		\$5.33		3.74		
VACCINATION ONLY										
Khatibi et al. (30)	Vaccination	3x	60%	100%	2013	IRR4181805	IRR439000000 251000000-842000000/ QALY	148.38	15608.94	Not cost-effective
Termrungruenglert et al. (31)	Vaccination	1x	80-100%	90-99%	2009	6,189–12,378 bhat	160,649-406394 baht/QALY	146.67-293.34	3807.32-9630.79	Cost-effective
Molina et al. (33)	Vaccination	3x	85-100%	48.4-96.8%	2013	\$13.10-13.79	\$843-925/DALY	11.64-12.25	749.00-821.85	Very cost-effective
Prinja et al. (32)	Vaccination	2x	70%	93%	2015		I\$3.38/DALY	3.19	3.19	Very cost-effective
VACCINATION AND SCREENING										
Sharma et al. (26)	Vaccination +	1x	80%		2005	I\$10-100	I\$2260- I\$3550/YLS	7.01-70.14	2980.86	Cost-effective
	VIA	1x		75-100%		I\$5.21		3.65		Cost-effective

	HPV DNA	2x	>60%	40-60%		I\$26.11	I\$4250/YLS	18.31		Very cost-effective
	Cytology	3x				I\$18.92		13.27		Not cost-effective
Sinanovic et al. (27)	Vaccination	3x	80%	90%	2007	\$281-289	\$1078-1460/QALY	209.09-215.04	802.13-1086.38	Cost-effective
	VIA					\$75		55.81		
	HPV DNA					\$309		229.93		
	Cytology					\$93		69.20		
Chanthavilay et al. (28)	Vaccination	3x	70(30–80)	Lifelong	2013	I\$33.5	I\$2544/DALY	29.76	2260.31	Very cost-effective
	VIA or	1x	50(10-80)%	73.2(66.5–80.0%)		I\$26.45	I\$351-2544/DALY	23.50	311.86-2260.31	Very cost-effective
	HPV DNA	2x	50(10-80)%	81.5(76.5–85.8%)		I\$47.18	I\$2102-4391/DALY	41.92	1867.6-3901.35	Cost-effective
	Cytology	3x	50(10-80)%	59(29–82%)		I\$48.27	I\$3455/DALY	42.89	3069.72	Cost-effective
Ezat and Aljunid (8)	Vaccination				2005	RM300-700	RM35347/QALY	60.98-142.31	7185.64	Cost-effective
	Cytology		70(40-90)%			RM41-72	RM947/QALY	8.33-14.64	192.53	Very cost-effective
Vanni et al. (29)	Vaccination	2x	50-90%	Lifelong	2008	\$30-676	\$13576/QALY	19.34-435.76	8751.21	Very cost-effective
	Cytology		63%	58%						

DNA deoxyribonucleic acid, *HPV* human papilloma virus, *ICER* incremental cost-effectiveness ratio, *ICUR* incremental cost-utility ratio, *DALYs* Disability-adjusted-life-years, *NCI* National Cancer Institute, *QALYs* quality-adjusted-life-years, *VIA* visual inspection with acetic acid, *YLS* years of life saved

HPV vaccination combined with screening

Combining HPV vaccination with any of the screening approaches potentially results in better cost-effectiveness outcomes as reported in four studies when compared with either screening only or vaccination only interventions (8,28,29). However, vaccination appears to be cost-effective only when combined with either VIA or HPV DNA testing but not in combination with cytology (ICER: I\$2980.86/ YLS (26).

Vaccination combined with VIA screening was associated with the highest (85.70%) decrease in cervical carcinoma cases (28) whereas two-times HPV DNA testing recorded the lowest (26-50%) reduction in cancer cases. When ranked based on the incremental cost-effectiveness ratios, there is an overlap of the ICERs across the three interventions namely screening only (ICERs I\$37.4-I\$210.41/YLS), vaccination combined with screening (ICERs I\$192.53-I\$8751.21 per QALY/ DALY/ YLS), and vaccination-only interventions (ICERs I\$3.19-I\$15608.94/QALY/ DALY).

The findings suggest that combining VIA screening and HPV vaccination could be the most cost-effective approach in reducing the lifetime risk for cervical neoplasms linked to HPV by 85.7% (28). Regarding the approach that could be most cost-efficient between screening interventions and vaccination programmes, probabilistic sensitivity analyses of cost-effectiveness results revealed that five yearly screening had a 70-80% probability for better cost-effectiveness in comparison with HPV vaccination programmes (28).

Discussion

The results from this review suggest HPV vaccination and screening interventions have potential cost-effectiveness in decreasing the lifetime risk as well as mortality (26-85.7%) associated with cervical carcinoma. The interventions are useful in mitigating the huge disease and economic burden caused by HPV infections. Prevention approaches namely screening, vaccination, or vaccination combined with screening are potentially cost-effective. The interventions become even more cost-effective when screening and vaccination programmes are combined. The findings are in tandem with a previous review, which reported vaccination only programmes are cost-effective even in settings that lack organized screening interventions (15).

Based on the outcomes of sensitivity analyses conducted across the studies, the findings revealed a host of factors that significantly influence the cost effectiveness of either screening or HPV vaccination interventions. Key among these factors is the age for delivering the vaccination or screening programmes as well as the number of doses or visits required for vaccination and screening respectively. With regard to vaccination age, the evidence suggests better outcomes with interventions delivered between the age of nine and fifteen years. However, there was insufficient evidence to conclude whether the different dose schedules influence the cost-effectiveness outcomes for HPV vaccination. Regarding screening interventions, two studies revealed that early screening from twenty years is more cost-effective in comparison with screening from thirty years and above (28,34).

The reviewed evidence also suggests that high coverage for both screening and HPV vaccination interventions are critical factors that influence cost-effectiveness outcomes. The interventions appear to be less cost-effective at a coverage below 50% of the population at risk. Regarding the potential impact of test sensitivity on HPV screening outcomes, the

findings are inconclusive due to contradictory results from the included studies. One study concluded that the sensitivity of the test used has negligible impact on the cost-effectiveness outcomes for screening interventions (35) while another contradicted these findings (28). The remainder of the studies did not conclude on the impact of the screening test sensitivity on the cost-effectiveness results.

Policy and practice implications

The findings of this review suggested that implementing organized programmes as opposed to opportunistic interventions potentially yields better cost-effectiveness outcomes due to improved coverage (28,34). This is consistent with the WHO recommendations emphasizing on the need for organized screening and vaccination interventions for better outcomes (40). Similarly, evidence from high-income countries demonstrates the importance for organized programmes (41).

The cost-effectiveness of screening and HPV vaccination interventions also depends on the screening method used, number of visits required, screening age, coverage, test sensitivity and specificity, as well as any follow-up requirements. Generally, any of the three screening methods (VIA, HPV DNA testing, and cytological testing or Pap smear) are cost-effective as a stand-alone intervention. However, combining screening interventions with a vaccination programme yields superior cost-effectiveness outcomes. Comparatively, VIA seems to be the most cost-effective screening strategy whereas the cytological testing seems to be least cost-effective when implemented alone or in combination with HPV vaccination. One of the factors that makes VIA significantly more cost-effective than other screening methods is its reduced loss-to-follow-up (LTFU) (28,35).

LTFU is of great importance especially in cases where there are confirmed positives following a screening test who do not turn-up for further testing and treatment (34). This also

applies to HPV vaccination interventions that require women to return to the facility for booster doses before attaining full immunity. LTFU increases the mortality rates therefore making a particular screening test less cost-effective. Therefore, public health practitioners should take into account the potential LTFU when choosing the most suitable screening method. In addition, there is need for relevant policy guidelines aimed at reducing the high LTFU witnessed in LMICs by opting for screening and HPV vaccination interventions that do not require women to frequent the health facility.

The success of a VIA screening intervention depends on the context and may suffer some setbacks caused by cultural barriers that undermine women's adherence (8). Notably, decision makers should have a clear understanding of the contextual factors such as women's preferences regarding the available screening methods. It may be prudent to opt for other culturally acceptable interventions that do not discourage women from taking up screening such as HPV DNA testing through a self-collection of HPV samples approach (35). Such an approach may be more costly when compared with sample collection by healthcare providers but useful in overcoming certain cultural barriers to cervical screening (35,42,43).

The reviewed evidence also suggests that providing screening at an early age of twenty (20) years has a higher cost-effectiveness and better outcomes in comparison with screening women after they attain 30 years (28),(34). This is important considering the fact that most screening interventions target women after attaining 30 years despite the evidence showing a peak incidence of HPV infection below this age (6,34).

Similarly, age influences the cost-effectiveness of immunization programmes targeting HPV eradication. Consistent with current evidence (44), this SR affirms that immunizing girls at an early age (9-13 years) yields higher benefits in LMICs (26,28,31–33). However, one of the reviewed studies established that providing HPV vaccination to girls

aged 15 years was not a cost-effective option (30). Notably, the latter study lacked country data in model calibration, assumed a low coverage and had the highest cost estimates in comparison with other studies included in this review. There was also no evidence with regard to the potential cost-effectiveness of HPV vaccination in older women.

Generally, screening and HPV vaccination programmes with higher coverage tend to yield better cost-effectiveness outcomes. This is evidenced by the sensitivity analyses conducted across the selected studies revealing coverage as a critical factor in cost-effectiveness of the interventions (8,31,34).

One of the challenges identified in LMICs is the low coverage of cervical cancer prevention interventions (45). The interventions only surpassed the cost-effectiveness threshold at higher coverage above 50-70% (28) but this remains an uphill task considering the fragile healthcare system in LMICs. As discussed above, increased coverage is achievable through the implementation of organised interventions. A case example is Rwanda's vaccination campaign that attained a 93.23% coverage surpassing the recommended threshold for immunization programmes (46). Considering the evidence that HPV vaccination and screening have potential cost-effectiveness even as stand-alone interventions, progressively increasing coverage through organised programmes can significantly reduce the risk for cancer and associated deaths.

The unit cost of vaccines is another key determinant influencing cost-effectiveness outcomes for HPV vaccination interventions in LMICs (27,32). For instance, doubling the unit price of HPV vaccine in Thailand would make the programme non cost-effective (31). Higher costs may limit the coverage of vaccination interventions within the context of LMICs. This may also translate to an increase in taxation as well as a rise in out-of-pocket expenditure to cover for the additional costs. This further worsens the economic burden of

cervical carcinoma associated with HPV infections and perpetrates the cycle of poverty in impoverished societies.

Implications for research

Additional studies are essential in ascertaining whether including males in HPV vaccination interventions influences the cost-effectiveness outcomes in LMICs. The evidence reviewed was not conclusive on this aspect considering that most included studies never incorporated the potential effect of including males during the model calibration process. One study reported that vaccinating males is a less attractive option (29) whereas another study argued that vaccinating males has no usefulness in settings that have 100% HPV vaccination coverage amongst females (31). This contradicts available evidence, which demonstrates that inclusion of males is a highly beneficial strategy in decreasing the lifetime risk of HPV associated infections (41,47), hence worth further investigating.

There was no sufficient evidence to conclude whether the number of doses required to complete a vaccination programme against HPV influences the cost-effectiveness of vaccination interventions. Across all the studies, subjects acquired lifelong immunity upon completion of the immunization schedule regardless of the number of doses. It is important to note the uncertainty in lifelong immunity considering the fact that there are no lifetime studies conducted to that effect considering the recent rollout of HPV vaccination programmes in 2007. Based on immunization guidelines from the CDC and the WHO, the doses required to achieve lifelong immunity are dependent upon the type of vaccine used and the age of vaccination (44,48).

Limitations

This review has a number of limitations that would significantly influence the generalizability of the findings. The studies included in the final synthesis varied significantly in terms of their contexts, perspective, population, costing approaches, and measurement of effects employed by the researcher. Most of the included studies were devoid of country-based data on the age-specific incidence of HPV infections making it impossible to develop an accurate model for HPV's natural history and cervical carcinogenesis.

Lastly, only one of the included studies used a dynamic model and accounted for the potential influence of herd immunity on the cost-effectiveness outcomes. Considering the high coverage of vaccination intervention assessed by the included studies, it would be prudent to assess the influence that herd immunity exerts on the cost-effectiveness outcomes. It is possible that the effects of the interventions that relied on the government perspective were overestimated because they did not take into account the costs associated with access to services as well as women's waiting times.

Conclusions

This SR synthesized the existing evidence with regard to the potential cost-effectiveness of cervical screening and HPV vaccination within the context of LMICs. The reviewed evidence suggests that HPV vaccination and screening interventions may be cost-effective in reducing the lifetime risk, economic burden, and mortality caused by HPV linked cervical carcinoma. In addition, combining HPV vaccination with VIA screening has potential for better cost-effectiveness outcomes within the context of LMICs in comparison with either screening or vaccination only programmes. The cost-effectiveness outcomes of HPV vaccination and screening interventions are dependent on age, screening method used, intervention coverage, and the number of doses or visits required for vaccination and screening respectively. There is need for additional studies on the duration of protection

achieved by the different dose schedules of HPV vaccines as well as the inclusion of boys in the vaccination programme.

Data availability

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request through bernardokeah@gmail.com or c.h.ridyard@bangor.ac.uk.

Authors contributions

B.O. conceived the idea, designed the study protocol and was the first reviewer. C.R. verified the study protocol, was the second reviewer and supervised the study. The authors discussed the findings of this study and contributed to the final report.

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Conflict of interest

No potential conflicts of interest

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Appendix 1: Search strategy (MEDLINE).

(((((((((developing countries) AND uterine cervical neoplasms)) AND ((hvp OR human papillomavirus OR papillomaviridae)))) AND (((((((screen*) OR test*) OR check*) OR monitor*) OR triag*)) OR (("visual inspection") OR cytology) OR ((papanicolaou OR pap smear)))))) OR (((((((developing countries) AND uterine cervical neoplasms)) AND ((hvp OR human papillomavirus OR papillomaviridae)))) AND (((vaccin*) OR immun*) OR innoculat*))) AND (((((cost-effective* OR cost effective*)) OR ((cost-benefit* OR cost benefit*)) OR ((cost-utility OR cost utility))) AND (hasabstract[text] AND ("2008/01/01"[PDAT] : "2018/12/31"[PDAT]) AND Humans[Mesh])

Appendix 2: Search history (MEDLINE)

S33	S23 AND S27	Limiters - Date of Publication: 20080101-20181231; Abstract Available; English Language Search modes - Boolean/Phrase
S32	S23 AND S27	Limiters - Date of Publication: 20080101-20171231; Abstract Available; English Language Search modes - Boolean/Phrase
S31	S23 AND S27	Limiters - Abstract Available; English Language Search modes - Boolean/Phrase
S30	S23 AND S27	Limiters - Abstract Available; English Language Search modes - Boolean/Phrase
S29	S23 AND S27	Limiters - Abstract Available Search modes - Boolean/Phrase
S28	S23 AND S27	Search modes - Boolean/Phrase
S27	S24 OR S25 OR S26	Search modes - Boolean/Phrase
S26	cost-utility or cost utility	Search modes - Boolean/Phrase
S25	cost-benefit* or cost benefit*	Search modes - Boolean/Phrase
S24	cost-effective* or cost effective*	Search modes - Boolean/Phrase
S23	S17 OR S22	Search modes - Boolean/Phrase
S22	S5 AND S21	Search modes - Boolean/Phrase
S21	S18 OR S19 OR S20	Search modes - Boolean/Phrase
S20	innoculat*	Search modes - Boolean/Phrase
S19	immun*	Search modes - Boolean/Phrase
S18	vaccin*	Search modes - Boolean/Phrase
S17	S5 AND S16	Search modes - Boolean/Phrase
S16	S11 OR S15	Search modes - Boolean/Phrase
S15	S12 OR S13 OR S14	Search modes - Boolean/Phrase
S14	papanicolaou or papsmear	Search modes - Boolean/Phrase
S13	cytology	Search modes - Boolean/Phrase
S12	"visual inspection"	Search modes - Boolean/Phrase
S11	S6 OR S7 OR S8 OR S9 OR S10	Search modes - Boolean/Phrase
S10	triag*	Search modes - Boolean/Phrase
S9	monitor*	Search modes - Boolean/Phrase
S8	check*	Search modes - Boolean/Phrase
S7	test*	Search modes - Boolean/Phrase
S6	screen*	Search modes - Boolean/Phrase
S5	S3 AND S4	Search modes - Boolean/Phrase
S4	hpv or human papillomavirus or Papillomaviridae	Search modes - Boolean/Phrase
S3	S1 AND S2	Search modes - Boolean/Phrase
S2	(MM "Uterine Cervical Neoplasms")	Search modes - Boolean/Phrase
S1	(MM "Developing Countries")	Search modes - Boolean/Phrase